

### **Remarks/Argument**

#### **Status of the Claims**

Claims 1-38 are in the application.

Claims 1-24 (in part), 25-28 and 33-38 have been withdrawn from consideration.

Claims 1-24 have been objected to.

Claims 1-24 and 29-32 have been rejected.

By way of this amendment, claims 25-28 and 33-38 have been canceled without prejudice, claims 1-24 and 29-32 have been amended and new claims 39-42 have been added.

Upon entry of this amendment, claims 1-24, 29-32 and 39-42 will be pending.

#### **Summary of the Amendment**

The specification has been amended, claims 25-28 and 33-38 have been canceled without prejudice, claims 1-24 and 29-32 have been amended and new claims 39-42 have been added.

The specification has been amended to more clearly refer to the cellular protein referred to as GCC. In particular, the definition of "GCC" that appears in the specification as filed on page 4 lines 24-29, which is paragraph [0013] of the published specification, has been substituted with a new paragraph that clearly indicates that GCC refers to guanylin cyclase C. Although Applicants' amendment incorporates the phrase "guanylin cyclase C" into the definition of GCC, and therefore makes the specification more clear, the specification provides full support for the amendment and one skilled in the art would readily recognize and understand that "GCC" refers to guanylin cyclase C prior to Applicants' amendment. No new matter has been added.

In particular, support for the amendment to the specification is found in the next paragraph of the specification; *i.e.*, page 5, lines 1-8, which states:

The nucleotide sequence encoding human GCC protein is disclosed in F. J. Sauvage et al. 1991 J. Biol. Chem. 266:17912-17918, each of which is incorporated herein by reference.

That reference refers to human guanylin cyclase C.

Additionally, the specification at page 10, lines 25 to page 11, line 5, states (emphasis added):

U.S. Pat. No. 5,518,888 issued May 21, 1996 to Waldman, PCT application PCT/US94/12232 filed Oct. 26, 1994, U.S. application Ser. No. 08/467,920 filed Jun. 6, 1995, and U.S. application Ser. No. 08/583,447 filed Jan. 5, 1996, which are each incorporated herein by reference, disclose that metastasized colorectal tumors can be targeted for delivery of active compounds by targeting ST receptors (**also referred to as guanylin cyclase C or GCC**).

It is clear from the specification that GCC refers to guanylin-cyclase-C, and those having ordinary skill in the art would readily recognize that GCC as used in the specification refers to guanylin cyclase C. Accordingly, the amendment of the specification does not introduce new matter.

Claims 1, 9, 10, 11, 20 and 21 have been amended to delete reference to non-elected subject matter, stomach cancer.

Claims 1-4, 11-14, 21-24 and 29-32 have been amended to replace the abbreviation "GCC" with the term the abbreviation refers to: "guanylin cyclase C." Support for the amendment is found in the passages of the specification set forth above. No new matter has been added.

Claims 1 and 11 have been amended to more clearly describe the invention. As amended, claims 1 and 11 more clearly refer to esophageal cancer cells as expressing guanylin cyclase C. Support for the amendment is found throughout the specification and claims as filed. No new matter has been added.

New claims 39 and 40 refer to specific embodiments dependent on claim 1 and claim 11 respectively. No new matter has been added.

New claims 41 and 42 refer to methods of diagnosing esophageal cancer using a photoactive imaging technology as the detectable moiety for identifying the present of guanylin cyclase C protein in esophageal tissue. The photoactive agent is linked to a guanylin cyclase C binding moiety in a conjugated compound that is contacted with the esophageal tissue. Upon exposure to light any conjugated compound bound to the esophageal tissue and therefore bound to the guanylin cyclase C present on the esophageal tissue will be detectable. Support for new claims 41 and 42 is found on page 45, line 25 to page 46, line 16 of the specification. No new matter has been added.

#### **Election/Restrictions**

Applicants acknowledge that the restriction requirement has been made final and that the subject matter related to stomach cancer has been withdrawn from consideration.

### **Specification**

Claims 1-24 have been objected to because the claims include non-elected subject matter, stomach cancer.

Applicants have amended claims to delete references to the non-elected subject matter. The basis for the objection has been obviated and the objection should be withdrawn.

### **Claim Rejection – 35 USC §112, second paragraph**

Claims 1-24 and 29-32 have been rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is asserted that claims 1-24 and 29-33 are unclear because it is not exactly clear what “GCC” encompasses. The definition of GCC appearing on page 4 lines 24-29 is reproduced in the official action. Based upon this definition, it is asserted that one of ordinary skill in the art would conclude that it is clear what constitutes or encompasses GCC.

Applicants respectfully urge that when the specification is read in its totality, one having ordinary skill in the art will clearly, immediately and unambiguously recognize that GCC refers to guanylin cyclase C. The specification expressly refers to the interchangeability to the terms “GCC,” “ST receptor” and “guanylin cyclase C” on page 10, lines 25 to page 11, line 5. Applicants have amended the definition of GCC to expressly recite that this abbreviation refers to guanylin cyclase C. However, Applicants respectfully urge that based upon the specification as filed one of ordinary skill in the art would immediately recognize that the references to GCC do in fact refer to guanylin cyclase C.

In addition to amending the specification, the claims have been amended to replace the abbreviation GCC with the full phrase “guanylin cyclase C.” No new matter has been added.

The claims are clear and definite and set forth the metes and bounds of the claimed subject matter. The claims are in compliance with the second paragraph of 35 USC §112. Applicants respectfully request that the rejection of claims 1-24 and 29-32 under 35 USC §112, second paragraph be withdrawn.

### **Claim Rejection – 35 USC §112, first paragraph Written Description**

Claims 1-24 and 29-32 have been rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. It is asserted that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of ordinary skill in the relevant art, at the time the application was filed, that the inventors had possession of the claimed invention. It is asserted that the meaning of GCC is unclear from the specification and therefore, in the absence of structural limitations, reference to GCC fails to adequately meet the written description requirement. Applicants respectfully disagree.

Applicants respectfully urge that it is clear from the specification that, at the time the application was filed, Applicants were referring to guanylin cyclase C in reference to the claimed subject matter. The specification fully and completely reflects that the abbreviation GCC refers to guanylin cyclase C. Applicants have amended the specification and the claims to further clarify this.

The claims are in compliance with the first paragraph of 35 USC §112. Applicants respectfully urge that the rejection of claims 1-24 and 29-32 under 35 USC §112, first paragraph, as failing to meet the written restriction requirement should be withdrawn.

**Claim Rejection – 35 USC §112, first paragraph  
Enablement**

Claims 1-24 and 29-32 have been rejected under 35 USC §112, first paragraph as failing to comply with the enablement requirement. It is asserted that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is pointed out that one of ordinary skill in the art must determine what can be considered GCC. As discussed above, GCC clearly refers to guanylin cyclase C and one of ordinary skill in the art would readily recognize this. One of ordinary skill in the art would be capable of determining whether or not a sample contains evidence of guanylin cyclase C gene expression without undo experimentation.

Regarding the predictability of the use of guanylin cyclase C as a marker of esophageal cancer, Applicants provide herewith a copy of a scientific publication, Park et al, (Aug 2002) Cancer Epidemiology, Biomarkers and Prevention, Vol. 11 pg. 739-744 (“Park”), which was published in refereed journal after the filing of the present application. Park refers to data showing the expression of guanylin cyclase C in the esophageal adenocarcinomas (see Table 2 on page 742). Park also states that “previous studies demonstrated that normal esophagus and stomach do not express . . . GCC” (see pg. 740, col. 2, last para.). As noted in the Official Action, Carrithers et al. 1996 PNAS 93: 14827 – 14832, which was cited in an Information Disclosure Statement filed July 12, 2001, refers to data indicating that guanylin cyclase C is not expressed in normal esophageal tissue. Taken together, these publications support the disclosure on pg. 11, lns. 15-17 of the present specification that the expression of guanylin cyclase C in esophageal tissue is correlated with esophageal cancer.

Claims 1-24 and 29-32 are fully enabled by the specification. One of ordinary skill in the art can make and use the present invention without undo experimentation. One having ordinary skill in the art would recognize that the practice of the present invention would be predictable based upon the disclosure and the state of the art.

The claims are in compliance with the first paragraph 35 USC §112. Applicants respectfully request that the rejection of claim 1-24, 29-32 under 35 USC §112, first paragraph, failing to comply with the enablement requirement be withdrawn.

**Claim rejection – 35 USC §102**

Claims 1-6, 9-16, 19-24 and 29-32 have been rejected under 35 USC §102(b) as being anticipated by Iannettoni et al. (Ann Thorac Surg. (1996)) 62: 1460-1466 or Wu et al. (Gastroenterology (1993) 105:837-844). It is asserted that given the alleged lack of description and clarity of GCC, the claims are interpreted as encompassing expression of any protein useful as diagnostic in esophageal cancer. It is asserted that Iannettoni and Wu teach that expression of sucrase isomaltase is diagnostic of esophageal cancer, and that sucrase isomaltase meets the limitation of the definition of GCC. Accordingly it is asserted that Iannettoni and Wu anticipate the claims. Applicants respectfully disagree.

As pointed out above, the specification makes clear that GCC refers to guanylin cyclase C. The claims clearly refer to guanylin cyclase C. Neither Iannettoni nor Wu refer to guanylin cyclase C in connection with esophageal cancer. In order to anticipate a claim, each and every limitation must be found in the reference. Since neither Iannettoni nor Wu refer to guanylin cyclase C, neither reference contains the limitation and thus neither reference anticipates the present invention.

Applicant's respectfully request that the rejection of claims 1-6, 9-16, 19-24 and 29-32 under 35 USC §102(b) as anticipated by Iannettoni et al or Wu et al be withdrawn.

**Claim rejection – 35 USC §103**

Claims 1-6, 9-16 and 19-24 have been rejected under 35 USC §103(a) as being unpatentable over Carrithers et al. (PNAS (1996) 93: 14827-14832). It is asserted that because the claims are drawn to screening an individual for the possibility that an individual may have primary or metastatic esophageal cancer by determining that GCC is expressed, and since Carrithers teaches guanylin cyclase C is not expressed in normal esophageal tissue, that therefore the presence of guanylin cyclase C can be used as a diagnostic marker for the possibility that an individual may have esophageal cancer cells. Applicants respectfully disagree.

Simply because Carrithers teaches that GCC is not expressed by normal esophageal tissue does not provide any suggestion or teaching that the presence of GCC in esophageal tissue would be useful as a marker for esophageal cancer. The mere fact that the GCC protein is not present in normal esophageal cells says nothing as to whether or not that same protein would be present in esophageal cancer cells. In fact, Carrithers teaches that GCC is not present in extraintestinal tissues or in tumors of non-intestinal origin (Carrithers, pg. 14830, col. 2 in the Discussion). Therefore, Carrithers teaches away from using GCC as a marker for cancers which are not of intestinal origin. Moreover, Carrithers showed that GCC transcript in normal intestinal mucosal tissue was similar to the GCC transcript in colorectal tumors (Carrithers, para. bridging pgs. 14829-14830). Thus, Carrithers teaches that the presence of GCC is not necessarily indicative of a cancerous state, but rather indicates that a cell is of colorectal origin whether that cell is normal or cancerous. Taken as a whole, one skilled in the art would not view Carrithers as teaching that the absence of GCC in a normal tissue means that cancerous cells derived from that tissue would

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express GCC. Rather, Carrithers teaches one skilled in the art that only normal or cancerous tissues of colorectal origin express GCC.

Applicants have deleted references in the claims to "possibility" and "may have," to remove confusing language. However, Applicants respectfully urge that Carrithers neither teaches or suggests the claimed invention, and that one having ordinary skill in the art comparing the teaching of Carrithers to the claimed invention would not find the use of GCC as a marker for screening for primary or metastatic esophageal cancer obvious.

Applicants respectfully request that the rejection of claims 1-6, 9-16 and 19-24 under 35 USC §103(a) as being unpatentable over Carrithers et al. be withdrawn.

### Conclusion

For the forgoing reasons, Applicants respectfully urge that claims 1-24 and 29-32 and new claims 39-42 are in condition for allowance. Applicants respectfully request that claims 1-24, 29-32 and new claims 39-42 be allowed. A Notice of allowance is earnestly solicited.

Respectfully submitted,

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Attachment

Park et al, (Aug 2002) Cancer Epidemiology, Biomarkers and Prevention, Vol. 11 pg. 739-744